REMARKS

Reconsideration of this application is respectfully requested. Claims 1 and 37 have amended to recite a modified release dosage form or tablet comprising (a) particles comprising (i) a solid carrier and (ii) tacrolimus dispersed in a vehicle, and (b) a modifying release agent. Claims 1 and 37 have further been amended to specify that the polyethylene glycol has a molecular weight of 1500 to 35000, and the particles have a d_{gw} of from about 50 to about 1000 µm. The preambles of claims 2-9, 20-25, 27-29, 31-36, 40-44 have been amended to recite a modified release oral dosage form. Claims 6, 7, 20, 23, and 35 have been amended for clarity. Claims 53-62 have been added. Support for these amendments can be found at, for example, paragraphs 15, 34, 44, 96, 99, 107, 113, 136, 153, 162, 169, 173, and 194 and Examples 1, 3, 10, and 14 of the published version of this application (US 2006/0287352) and original claim 10. Claims 10, 36, 51, and 52 have been canceled without prejudice. Claims 1-9, 20-25, 27-29, 31-35, 37, 40-44, and 53-62 are pending and at issue.

In-Person Interview on December 14, 2010

Applicants wish to thank Examiner Young and Supervisory Patent Examiner Hartley for the courtesies extended during the in-person interview on December 14th. During the interview, Applicants discussed the invention and its benefits over prior tacrolimus formulations, as well as the differences between the claimed invention and Koretke (WO 01/95939).

Obviousness Rejection Over Yamashita in view of Koretke

Claims 1-10, 20-25, 27-29, 31-37, 40-44, 51 and 52 stand rejected under 35 U.S.C § 103(a) as obvious over Yamashita (EP 1064942) in view of Koretke (WO 01/95939). According to the Examiner, Yamashita discloses a tacrolimus tablet with particulate components and PEG having a

molecular weight above 1500.[1] *See* page 4 of the June 7, 2010 Office Action. The Examiner acknowledges that Yamashita does not disclose a mixture of PEG and poloxamer. The Examiner contends that Koretke discloses controlled release formulations containing an active agent, PEG and a poloxamer and thus concludes that it would have been obvious to incorporate the Koretke hydrophilic components in the Yamashita tacrolimus formulation. Applicants respectfully disagree.

A. The Invention

The presently claimed invention is a modified release oral dosage form formed from tacrolimus containing particles and a modifying release agent. The particles comprise (i) a solid carrier and (ii) tacrolimus dispersed in a vehicle of polyethylene glycol (PEG) and poloxamer. The particles have a geometric weight mean diameter d_{gw} of from about 50 μm to about 1000 μm. Finally, the dosage form releases less than 20% w/w of the tacrolimus within 30 minutes under the conditions specified in the claims. The present inventors have surprisingly discovered that the presently claimed formulation provides enhanced bioavailability as well as lower fluctuation and swing than other tacrolimus formulations, including Advagraf which is a once-daily extended release tacrolimus formulation marketed by Astellas Pharma in Europe.

Tacrolimus is an immunosuppressant used to prevent organ rejection in patients who have received liver, kidney, or heart transplants. Tacrolimus, however, has a narrow therapeutic window. "Subtherapeutic tacrolimus blood concentrations increase the risk of transplant rejection enormously, while high tacrolimus blood concentrations may lead to severe side effects such as nephrotoxicity, neurotoxicity and hyperglycemia." Op den Buijsch, et al., *Fundamental & Clinical Pharmacology*, 21:427-435 (2007) (Exhibit A). It is, therefore, desirable to have a tacrolimus dosage form which provides consistent blood levels of tacrolimus in these patients. The presently claimed dosage form achieves this goal.

[1] The June 7, 2010 Office Action states that Yamashita discloses a controlled release tacrolimus formulation comprising various hydrophilic and hydrophobic components, and that the "hydrophilic components include [PEG] with a molecular weight of 4000 along with Gelucire polymers" (page 4, first full paragraph). Applicants' representative, however, has been unable to locate any disclosure in Yamashita of Gelucire polymers.

Two measurements for the consistency of a drug level include "fluctuation" and "swing." The results of a human clinical study comparing the presently claimed formulation to Advagraf is provided in Example 20 of US 2010/0105717 (Exhibit B, p. 33-36). (Both the present application and US 2010/0105717 are assigned to LifeCycle Pharma A/S.) Subjects were administered either one 2 mg tablet of the present invention (referred to as "LCP Tacro")[2] or two 1 mg capsules of Advagraf. The pharmacokinetic parameters of tacrolimus in the subjects was measured on day 10 and is reported in Tables 20-3 (LCP Tacro) and 20-4 (Advagraf) of US 2010/0105717 (p. 35). The fluctuation and swing measurements for LCP Tacro were nearly half that of Advagraf (shown below):

Parameter	LCP Tacro (Table 20-3)	Advagraf (Table 20-4)
Fluctuation (%)	60.92	106.46
Swing (%)	78.16	150.98

Additionally, the bioavailability of tacrolimus from LCP Tacro (AUC_{tau} = 133.99 ng·hr/mL) was about 50% greater than Advagraf (AUC_{tau} = 89.86 ng·hr/mL). *See also* Abstract #284 of the 2008 American Transplant Congress (ATC) (showing that the bioavailability of the presently claimed formulation has approximately 50% greater bioavailability than Advagraf after 10 days of treatment) (Exhibit C).

Notably, Advagraf appears to be similar to formulations described in Yamashita, which is assigned to Astellas Pharma (formerly known as Fujisawa Pharmaceutical). Advagraf contains hydroxypropyl methylcelluose (also known as hypromellose), ethylcellulose, lactose, and magnesium stearate.[3] Tacrolimus formulations in Examples 20 and 21 of Yamashita (formulations M, N, O, and P) also include these components.

[2] The formulation of LCP-Tacro is shown in the last table in the right column on page 36 of US 2010/0105717.

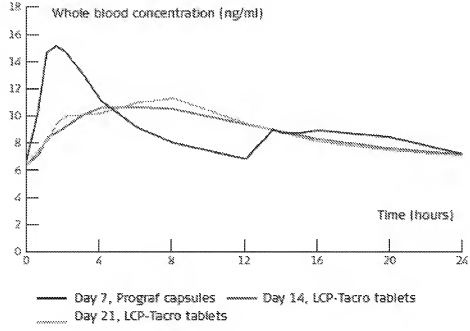
[3] The components in Advagraf are listed in the "Summary of Product Characteristics" for Advagraf at the European Medicines Agency (EMA) website. See http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/-medicines/000712/human_med_000629.jsp&mid=WC0b01ac058001d124&murl=menus/medicines/medicines.jsp&jsenabled=true.

The presently claimed formulation also provides a superior pharmacokinetic profile compared to Prograf, the other marketed formulation of tacrolimus by Astellas Pharma. (Prograf is marketed worldwide including the U.S.) Example 19 of US 2010/0105717 (Exhibit B, p. 27-33) describes the results of a clinical study involving 47 kidney transplant patients who prior to the study were being treated with Prograf (a twice daily formulation of tacrolimus). The patients were kept on Prograf for the first 7 days of the trial and then converted to the presently claimed formulation (again referred to as "LCP Tacro") at a ratio of 1 mg Prograf to 0.66-0.80 mg LCP-Tacro, without a further change in the dose of tacrolimus. The reduced amount of tacrolimus was used since it was previously determined that LCP-Tacro provides significantly greater systemic exposure to the tacrolimus. The bioavailability (AUC_t) of LCP Tacro was 37-39% greater than that of Prograf (using dose corrected data). *See* the table at the bottom of page 28 of US 2010/0105717. LCP Tacro also exhibited a significantly lower degree of fluctuation and swing compared to Prograf. The degree of fluctuation and swing were reduced by approximately 40% and 37%, respectively. These results are shown in the table below.

Parameter	Prograf	LCP Tacro	
	Day 7	Day 14	Day 21
AUC_t (ng·hr/mL)[4]	34.81	47.73	48.3
% increase relative to Prograf		37.12%	38.75%
Fluctuation (%)	127.41	73.24	77.04
% decrease relative to Prograf		42.52%	39.53%
Swing (%)	174.55	102.80	110.07
% decrease relative to Prograf		41.11%	36.94%

[4] The AUC_t values reported here for Prograf and LCP-Tacro are dose corrected values. As mentioned above, patients received 0.66-0.80 mg LCP-Tacro for each 1 mg of Prograf.

As shown by the clinical data above, the presently claimed formulation provides greater systemic exposure to tacrolimus with a lower degree of fluctuation and swing. Incredibly, the presently claimed formulation provides a nearly constant level of tacrolimus over 24 hours as shown by Figure 5 of US 2010/0105717 (reproduced below with modified ledger).



The "flat" pharmacokinetics provided by the presently claimed formulation avoids the peaks and valleys associated with Prograf and Advagraf, and therefore offers consistent pharmacokinetic profile and efficacy, and reliability of performance. Further, a lower effective dosage can be used compared to Prograf and Advagraf. The superior results achieved with the presently claimed formulation are not disclosed or suggested by Koretke or Yamashita.

Tacrolimus is a poorly soluble drug and, as a result, is difficult to make highly bioavailable. Astellas which has been working with tacrolimus for at least two decades developed Prograf and Advagraf and would therefore have had the motivation to have developed and brought to market a formulation with greater bioavailability. Astellas' currently marketed products, Prograf and

Advagraf, however, have significantly lower bioavailability and therefore require doses at least 25% greater than the presently claimed formulation to achieve similar bioavailability.

B. Structural Difference Between the Present Invention and Koretke and Yamashita

Neither Koretke nor Yamashita disclose or suggest particles containing (i) a solid carrier and (ii) tacrolimus dispersed in a vehicle of PEG and poloxamer. In Koretke, the poorly soluble drug is co-melted with PEG and poloxamer and poured into a capsule (see, for example, p. 7, lines 8-26, of Koretke). Koretke does not form particles where each particle includes a solid carrier (such as lactose) with tacrolimus dispersed in PEG and poloxamer. Koretke also does not disclose drug containing particles having a geometric weight mean diameter d_{gw} of from about 50 to about 1000 μm.

Yamashita does not disclose poloxamer. Additionally, Yamashita does not disclose or suggest that particles containing a solid carrier and tacrolimus dispersed in PEG and poloxamer could provide enhanced bioavailability and would be well suited for preparing an extended release formulation which provides a substantially flat pharmacokinetic curve as discussed above.

C. Tacrolimus is Unsuitable for the Delivery System in Koretke

The applicants have further found that tacrolimus is unsuitable for use in Koretke's delivery system. As discussed in greater detail below, Koretke requires that the drug be melted without decomposition. Tacrolimus, however, readily degrades when heated to its melting point yielding a product unsuitable as a pharmaceutical.

Koretke repeatedly states that his delivery system is only suitable for drugs that melt without decomposition below the flashpoint of polyethylene glycol.

> [T]his invention is useful for **any poorly water soluble, poorly wetable compound that melts without decomposition** below the flash point of polyethylene glycol.

(Koretke, p. 4, lines 22-24, emphasis added)

> The instant compositions consist essentially of ... **a drug which melts without decomposition** at a temperature below the flashpoint of the PEG.

(Koretke, p. 4, lines 26-28, emphasis added)

> **The drug should melt without decomposition** at a temperature below the flashpoint of the PEG.

(Koretke, p. 5, lines 5-6, emphasis added)

> [T]his invention relates to a solid dispersion pharmaceutical composition consisting essentially of a co-melt of a poloxamer surfactant, a mid-molecular weight polyethylene glycol and **a therapeutically active compound that melts without decomposition** at a temperature below the flash point of polyethylene glycol.

(Koretke, p. 1, lines 7-11, emphasis added)

Importantly, this requirement inherently requires the drug to melt without decomposition. (In any event, the flashpoint of PEG 6000 is about 246° C according to Koretke (Koretke, p. 6, lines 3), which is significantly higher than the ~126-130° C melting point of tacrolimus.)

Koretke also requires heating the drug to at least its melting point in the preparation of his solid dispersion. For instance, Koretke defines a "solid dispersion" as a material which is solid at room temperature, which was produced by "blending ***melted*** drug with" other components (Koretke, p. 4, lines 32-36, emphasis added). *See also* Koretke, p. 6, lines 25-27, emphasis added ("The fast release solid dispersions ... are preferably made by ***melting the drug***, the polyethylene glycol and the poloxamer surfactant together with mixing, to form a homogenous melt mixture"). The melting of the drug is necessary to convert it into an amorphous state, which is maintained by the PEG and poloxamer (Koretke, page 4, lines 1-3).

As discussed in the Declaration of Nikolaj Skak submitted herewith[5], the preparation process described in Koretke was repeated using Koretke's preferred components of PEG 6000 and poloxamer 188 at Koretke's preferred PEG-poloxamer-drug weight ratio of 15:1:4 (Koretke, p. 5, lines 33-37, p. 6, lines 4-6, and p. 7, lines 3-5; Skak Declaration, ¶4 and 6). The mixture of PEG, poloxamer, and tacrolimus was heated to the lowest end of the melting point range of tacrolimus (126° C), and the amount of tacrolimus and three degradation products were measured (Skak Declaration, ¶4-8). The experiment was repeated three times, and each product was analyzed twice (*id.*, ¶9). The results are shown in Table 2 on page 4 of the Skak Declaration.

About 14% of the initial amount of tacrolimus was lost during each run. Furthermore, about 2.2 to 2.5% of the tacrolimus degraded to its C8-epimer. According to ICH guidelines, pharmaceutical products are not permitted to have more than 0.5% of any single degradation product, unless additional studies have been performed and establish the safety of the degradation product at the elevated levels observed (Skak Declaration, ¶10). According to Mr. Skak, a pharmaceutical scientist with considerable experience,

> To my knowledge, neither the U.S. Food and Drug Administration nor the European Medicines Agency has found a tacrolimus product containing 2.4% or more of the C8-epimer to be safe based on such studies. Accordingly, such a product is not considered pharmaceutically acceptable. Because of the high level of degradation product and double digit reduction in tacrolimus, a skilled artisan would not consider the Koretke process viable for making pharmaceutical formulations of tacrolimus.

(*id.*)

Because tacrolimus undergoes significant degradation upon melting, a skilled artisan would not consider it suitable for use in Koretke's process.

[5] An unexecuted copy of the Declaration is being presently submitted. An executed copy of the Declaration will be submitted shortly.

D. There was No Motivation to Combine Koretke and Yamashita

A skilled artisan would not have combined the formulation of Koretke with that of Yamashita. Yamashita is directed to a *sustained release* formulation of a macrolide compound (abstract and paragraph [0003] (page 1)), while Koretke is directed to a *fast release* formulation (abstract; page 1, lines 4-5; page 2, lines 27-30).

> [The invention of Koretke] enables the solid dispersion to be a fast-release solid dispersion formulation, whereas typical solid dispersions enhance solubility, and therefore bioavailability, but are slow release formulations.

(Koretke, p. 3, lines 22-24). A skilled artisan reading Yamashita and Koretke would understand that the terms "sustained release" and "fast release" are relative to an immediate release dosage form of the durg. A skilled artisan would, therefore, not have had any motivation to incorporate a fast release formulation as taught in Koretke into the sustained release formulation of Yamashita. Further, unlike Koretke, the presently claimed tablet provides slow release of tacrolimus. Specifically, the presently claimed tablet releases less than 20% of the tacrolimus after 30 minutes under specified *in vitro* dissolution conditions.

Koretke is also completely silent regarding a tacrolimus composition of any kind, let alone a tacrolimus tablet, as presently claimed. Koretke merely discloses that his invention is useful for "any poorly soluble, poorly wettable compound that melts without decomposition below the flash point of polyethylene glycol." *See* Koretke at page 4, lines 22-24. Applicants submit that this blanket statement regarding compounds that may be used in the Koretke invention would not in any way lead one of ordinary skill in the art to select tacrolimus, as required by the present claims. Indeed, the only drug exemplified by Koretke is (S)-(-)-N-(α-ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide, which has a significantly different chemical structure and function than tacrolimus.

Moreover, there is no single method for solubilizing all poorly soluble drugs. As a result, numerous techniques have been developed for solubilizing such drugs. The effectiveness of these techniques varies considerably from drug to drug, and a formulator cannot predict which technique

will be successful. Accordingly, a skilled formulator would not have known based on Koretke that a mixture of PEG and poloxamer would be highly effective at delivering tacrolimus in a slow release formulation.

For the foregoing reasons, one of ordinary skill would not have had any motivation to incorporate the *fast* release composition of Koretke in the *sustained* release composition of Yamashita, or a reasonable expectation that a combination of PEG and poloxamer could successfully be used to prepare a high bioavailability, slow release tacrolimus tablet, as presently claimed.

E. Koretke Teaches Away From "Compressed" Dosage Forms as Recited in Claims 35, 37, and 60

Additionally, Koretke expressly teaches away from compressing his formulation. In particular, Koretke states that the alteration of his solid dispersion by physical means can result in an uncontrolled erosion rate and crystallization (nucleation) of the drug:

> Preferred solid dispersions of this invention may be filled into capsules or molds prior to solidification. Alteration of the solid dispersion by physical means (i. e., additional energy added) from the original cooled solid form yielded drastically different solubilization due to uncontrolled erosion rate and nucleation of the drug substance in the milled high surface area formulation. **This property distinguishes this invention from known solid dispersion dosage forms in which solid dispersion of drug and PEG were milled and filled into capsules or tableted.**

(Koretke, p. 6, lines 31-38, emphasis added). Thus, according to Koretke, alteration of the solid dispersion by physical means (such as by compression as recited in claims 35, 37, and 60) can yield "drastically different solubilization" of the drug.

For the reasons stated above, Yamashita and Koretke, taken alone or together do not render obvious the present claims. Applicants respectfully request, therefore, that the rejection be withdrawn.

Double Patenting Rejections

Claims 1-44 and 51 stand provisionally rejected for obviousness-type double patenting over (i) claims 59, 66, 72-74, 83-85 and 90 of copending application no. 10/574,125 ("the '125 Application") and (ii) claims 1, 3-11, 13-29, 31-34, 36, 37, 40-44 and 53-56 of copending application no. 10/569,863 ("the '863 application").

Terminal disclaimers over the '125 or '863 Applications were previously submitted on September 7, 2010. Accordingly, Applicants respectfully request that these provisional rejections be withdrawn.

Claims 1-44 and 51 stand provisionally rejected for obviousness-type double patenting over claims 1-50 of copending application no. 11/885,992 ("the '992 Application"). The '992 Application has been abandoned, rendering this rejection moot.

In view of the above amendments and remarks, Applicants believe the pending application is in condition for allowance. If there are any other issues remaining, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

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